Japanese Kokai Patent Application No. Sho 62[1987]-294679

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NOVEL ISOQUINOLINE DERIVATIVES

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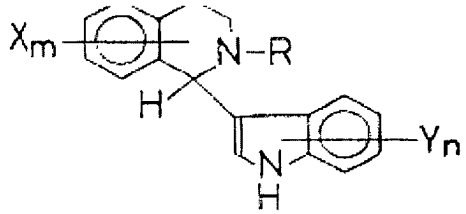
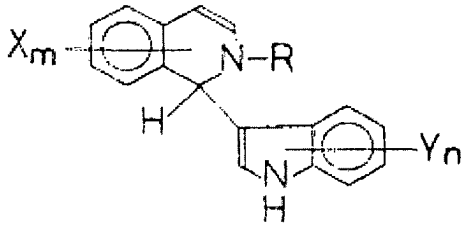
Claim

Novel isoquinoline derivatives represented by the following general formula (I) or (II),



(I)



(II)

(provided that X in the formulas represents an alkyl group, halogen or nitro group, Y represents an alkyl group, halogen, nitro group, amino group, hydroxyl group or carboxyl group and R represents an alkyl group, and m and n are integers of 0-2).

Detailed explanation of the invention

Industrial application field

This invention pertains to novel isoquinoline derivatives. Also, these compounds are useful as agricultural and horticultural bactericides or intermediates.

Prior art

Many reports have been published with respect to the addition reactions at position 1 of quaternary isoquinolinium salts, including for example, N-benzoylisoquinolinium salt (W. E. McEwen et al., Chem. Rev., 55, 511 (1955), N-benzylisoquinolinium salt (F. Brohnke, et

al., Chem. Ber., 90, 227 (1957) and N-methylisoquinolinium salt (N. J. Leonard et al., J. Am. Chem. Soc., 71, 3405 (1949), but no other N-alkylisoquinolinium salt except the aforementioned N-methyl derivatives is known.

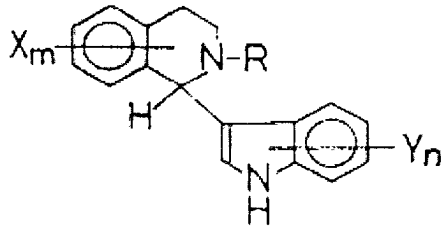
Also, Japanese Kokai Patent Application No. Sho 59[1984]-219,203 disclosed 1,2,3,4-tetrahydroisoquinoline derivatives and Sho 59[1984]-219,204 disclosed 1,2,3,4-tetrahydroisoquinolinium salt derivatives, but neither disclosed any 1-substituted isoquinoline derivatives.

Problems to be solved by the invention

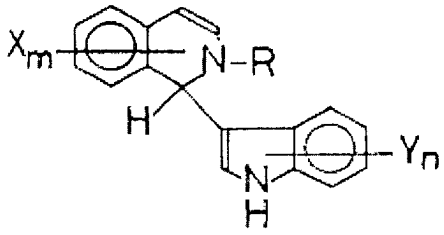
The present invention is based on the finding that isoquinoline derivatives such as those disclosed in the aforementioned Japanese Kokai Patent Application No. Sho 59[1984]-219,203 and Sho 59[1984]-219,203 [sic; 204] are effective against certain bacteria and fungi, and the objective lies in providing novel isoquinoline derivatives useful as agricultural or horticultural bactericides or intermediates, particularly the objective lies in providing novel isoquinoline derivatives by adding an indole backbone to position 1 of the isoquinoline backbone.

Means to solve the problems

Specifically, the present invention pertains to isoquinoline derivatives represented by the following general formula (I) or (II),



(I)



(II)

(provided that X in the formulas represents an alkyl group, halogen or nitro group, Y represents an alkyl group, halogen, nitro group, amino group, hydroxyl group or carboxyl group and R represents an alkyl group, and m and n are integers of 0-2).

In the isoquinoline derivatives of the present invention, chlorine and bromine are preferred when substituent X in the aforementioned general formulas (I) and (II) represent halogens, and a methyl group is preferred when it represents alkyl groups; also, the positions of the substituents are positions 3-8 of the isoquinoline backbone, and furthermore, the substituents may be the same or different if X represent 2 substituents. Also, with respect to substituent Y, a methyl group is preferred if it represents an alkyl group and bromine is preferred if it represents a halogen; also, the positions of the substituents are positions 2 and/or 4-7 of the indole backbone, and furthermore, the substituents may be the same or different if Y represent 2 substituents. Also, substituent R is preferably an alkyl group of 1-20 carbons and said substituents may optionally contain oxygen-containing groups such as a hydroxyl group and alkoxy groups, or it may contain unsaturated bonds such as ethylene bonds.

The compounds of the present invention represented by the aforementioned general formulas (I) and (II) can be produced by the following methods, for example.

Specifically, first of all, the nitrogen atom of the isoquinoline backbone is alkylated to prepare an N-alkylisoquinolinium salt using an alkylating agent such as an alkyl halide and said N-alkylisoquinolinium salt is reacted with indole in the presence of an alkali, and the reaction product obtained is extracted with an organic solvent, followed by washing to remove unreacted compounds and drying to remove the solvent, which results in the objective compound represented by general formula (II).

Next, the compounds of general formula (II) obtained in the aforementioned manner is hydrogenated with sodium borohydride or by contact hydrogenation in the presence of a platinum catalyst, for example, to produce the objective compounds of general formula (I).

The isoquinoline derivatives of the present invention obtained in the aforementioned manner are effective against various diseases that inflict significant damage on agricultural and horticultural cultivations, and the typical ones include bacterial diseases such as *Xanthomonas citri*, *Xanthomonas oryzae*, *Pseudomonas lachrym-ans* and *Erwinia aroideae* and fungal diseases such as *Cochliobolus miyabeanus*, *Piricularia oryzae*, *Diaporthe citri*, *Alternaria mali*, *Phytophthora parasitica* and *Glomerella phomoides*. Among them, the compounds of the present invention are particularly effective against the important but difficult to eradicate diseases of citrus plants, the bacterial *Xanthomonas citri* and the fungal *Diaporthe citri*, so that there is no need to spray chemicals for the 2 diseases individually, simplifying the operation and making the compounds extremely useful. In this respect, the compounds of the present invention also have the activities of insecticides including anti-tick agents so that they can be utilized for this purpose.

When the compounds of the present invention are utilized as agricultural bactericides, surfactants, solvents, diluents, dispersants, emulsifiers, wetting agents, adsorbing agents, thickeners, fertilizers and other liquid or solid carriers may be incorporated to produce

preparations in the forms of easy application as agricultural chemicals; examples of the form of the agricultural preparations include hydrated products, emulsions, aqueous solution, powder and water surface-dispersive oily preparation and granules, and all forms of preparation can be utilized.

Application examples

The present invention is described based on the following application examples, preparation examples and experimental examples.

I. Application examples

Application Example 1

Production of the compounds represented by general formula (II)

Isoquinolines (39 mmol) shown in Table 1 and alkyl halides (43 mmol) shown in Table 1 were dissolved in dimethyl formamide 5 mL, and the mixture was reacted at 150°C for 5 h. The dimethyl formamide in the reaction mixture was removed by vacuum distillation using a glass tube oven, and the residue was washed with isopropyl ether, and alkylisoquinolinium salts were obtained at yields shown in Table 1.

The obtained alkylisoquinolinium salts 3 g and purified indole (molar ratio 0.9 versus alkylisoquinolinium salt) were dissolved in acetonitrile 30 mL, and equal moles of 10 wt% potassium hydroxide versus the alkylisoquinolinium salt was added dropwise while the mixture was stirred at room temperature or on an ice bath; after reacting for 30-60 min, the reaction mixture was transferred to a separatory funnel and the oily layer between the upper acetonitrile layer and the lower aqueous layer was separated and dissolved in dichloromethane or chloroform, followed by washing with water and then drying over sodium sulfate. The solvent was removed at a temperature below 40°C and the objective products represented by general formula (II) were obtained. The products obtained were all in grease form with reddish-brown color. Also, Table 1 shows the crude yields, purities of the objective products represented by general formula (22), and the ^{1}H-NMR chemical shifts (δ: ppm) for the methylene hydrogen of the alkyl groups bonded to the N atom at position 2 of the isoquinoline backbone.

Table 1

① 化合物 No.	② アルキルハライドの種類	③ イソキノリンの種類	④ 四級塩の収率 (wt%)	⑤ 式(II)化合物 粗収率 (wt%) (5a)	⑤ 式(II)化合物 純度 (wt%) (5b)	⑥ ^{1}H-NMR δ (ppm) (α位)
1	CH_3 Cℓ	⑦ 精製イソキノリン	46	−	15	3.5
2	C_3H_7 Cℓ		75	95	24	3.0
3	C_6H_{13}Cℓ		85	95	31	3.0
4	C_8H_{17}Cℓ		92	79	66	3.0
5	$C_{12}H_{25}$Cℓ		71	92	47	3.0
6	$C_{14}H_{29}$Cℓ		80	90	56	3.0
7	$C_{16}H_{33}$Cℓ		99	77	47	2.9
8	$C_{18}H_{37}$Cℓ		80	77	43	2.9
9	$C_{18}H_{35}$Cℓ		82	92	44	3.0
10	HOC_2H_4 Cℓ					
11	C_6H_{13}Cℓ	⑧ 4-ブロモイソキノリン	99	97	94	3.0
12	C_8H_{17}Cℓ		60	78	84	3.0
13	$C_{12}H_{25}$Cℓ		35	87	50	3.0
14	$C_{14}H_{29}$Cℓ		43	−	35	−
15	$C_{18}H_{37}$Cℓ		32	58	35	−

Key
1 Compound
2 Type of alkyl halide
3 Type of isoquinoline
4 Yield of quaternary salt
5 Compound of formula (II)
5a Crude yield
5b Purity
6 α position
7 Purified isoquinoline
8 4-Bromoisoquinoline

Furthermore, Table 2 shows the more detailed analytical results of ^{1}H-NMR, ^{13}C-NMR and mass spectra of compound No. 4 and No. 11 shown in the aforementioned Table 1. In this respect, α for ^{1}H-NMR and ^{13}C-NMR in Table 2 represents the position of the carbon atom

bonded to the N atom of the isoquinoline backbone, ① represents position 1 of the isoquinoline backbone, ③ represents position 3 of the isoquinoline backbone, ④ represents position 4 of the isoquinoline backbone and ②' represents position 2 of the indole backbone, respectively.

Table 2

① 化合物 No.	^{1}H−NMR				^{13}C−NMR		MS
	α	③	④	②'	α	①	(m/e)
4	3.0	5.5	6.4	6.4	52.5	69.7	358
11	3.0	6.6	—	6.4	52.6	69.5	409

Key 1 Compound

Also, compounds represented by general formula (II) were produced in the same aforementioned manner except that laurylisoquinolinium chloride was utilized as the alkylisoquinolinium salt and indole derivatives shown in Table 3 were utilized to replace purified indole and the products were extracted with carbon tetrachloride and separated by chromatography and purified by vacuum distillation at normal temperature, followed by drying. Table 3 shows the yields and the properties of the products obtained.

Table 3

① 化合物 No.	② インドール類の種類（置換基のみで表示する。）	③ 一般式（Ⅱ）化合物	
		④ 収率 (wt%)	⑤ 性状
16	5-クロロ ⑥	29.4	赤褐色オイル状 ⑦
17	6-ニトロ ⑧	64.6	〃
18	5-ヒドロキシ ⑨	56.6	赤褐色グリス状 ⑩
19	4-ヒドロキシ ⑪	53.8	赤褐色オイル状 ⑦
20	7-メチル ⑫	46.2	〃
21	5-アミノ ⑬	25.8	茶褐色オイル状 ⑭

Key 1 Compound
2 Type of indole (shown by the substituents only)
3 Compound of general formula (II)

4 Yield
5 Property
6 5-Chloro
7 Reddish-brown oil
8 6-Nitro
9 5-Hydroxy
10 Reddish-brown grease
11 4-Hydroxy
12 7-Methyl
13 5-Amino
14 Brownish oil

Application Example 2

Production of the compounds represented by general formula (I)

N-Alkylisoquinolinium halides having R alkyl groups shown in Table 4 and purified indole were dissolved in methanol or acetonitrile, and 28 wt% CH_3ONa methanol solution or 10% aqueous KOH solution was added to this solution, and the mixture was reacted for about 2 d. The solvents in the reaction product were removed by distillation and the residue was treated with Amberlist and then reduced with $NaBH_4$. Afterward, the reaction product was subject to purification with a silica column (elution solvent chloroform), and compounds of general formula (I) with substituents X, Y and R shown in Table 4 were obtained. The products obtained were all yellowish-brown oily substances and Table 4 shows the yields and properties; also, Table 5 shows the analytical results of ^{13}C-NMR and mass spectra of compound No. 22 and No. 23. With respect to the data for ^{13}C-NMR, α, ①, ③ and ④ are the same as in Table 2, while ③' represents position 3 of the indole backbone.

Table 4

① 化合物 No.	② 一般式（I）化合物 R	X	Y	③ 収率 (%)
22	CH_3	H	H	79
23	C_8H_{17}	H	H	75
24	$C_{12}H_{25}$	H	H	65
25	$C_{14}H_{29}$	H	H	80
26	$C_{12}H_{25}$	H	5-OH	60

Key 1 Compound
2 Compounds of general formula (I)

3 Yield

Table 5

① 化合物 No.	$^{13}C-NMR$ α	①	③	④	③′	MS (M/1)
22	44.0	62.5	51.4	29.0	116.5	262
23	54.1	60.3	46.5	31.8	110.9	360

Key 1 Compound

II. Preparation examples

(1) Emulsion

No. 1 compound	10.0 wt%
Xylol	86.5 wt%
Emulgen 909 (Product name of KAO Soap K.K.)	2.0 wt%
Neo Pelecks [transliteration] C70 (Product name of KAO Soap K.K.)	1.5 wt%

An emulsion was prepared by mixing the aforementioned chemicals until homogeneous, which can be utilized as is or in diluted forms.

(2) Hydrated preparation

No. 11 compound	20.0 wt%
Neo Pelecks No. 6F (Product name of KAO Soap K.K.)	3.0 wt%
Sorbol 8070 (Product name of Toho Chemical K.K)	4.0 wt%
White carbon	5.0 wt%
Clay	68.0 wt%

A hydrated preparation was prepared by pulverizing and mixing the aforementioned chemicals until homogeneous, which can be utilized by diluting with water or mixing with soil.

(3) Powder preparation

No. 15 compound	5.0 wt%
Talc	95.0 wt%

A powder preparation was prepared by pulverizing and mixing the aforementioned chemicals until homogeneous, which can be utilized as is or by mixing with soil.

III. Experimental example

(No. 1) Potted plant experiment on *Cochliobolus miyabeanus*

A chemical solution of 1000 ppm concentration was spread thoroughly on rice plants (variety: Tonewase) in pots and the solution sprayed was air-dried for 1 d, and a spore suspension of *Cochliobolus miyabeanus* (spore concentration (150-fold): 6-8 spores per vision field) was sprayed and inoculated, followed by standing at 25°C in a humid room for 24 h, and the number of diseased lesions per leaf was counted after 1 week and evaluation was performed using 3 levels, namely A: inhibitory rate greater than 95%, B: inhibitory rate 50-95% and C: inhibitory rate less than 50%. Table 6 shows the results.

Table 6

① 化合物 No.	試験例 ② No.-1	No.-2	No.-3
2	A	A	–
3	A	A	–
4	A	A	A
5	A	A	A
6	A	A	A
7	A	A	A
8	A	A	–
9	A	A	–
10	A	A	–
11	A	A	–
12	A	A	A
13	A	A	A
15	A	A	A
24	–	A	–
25	–	A	–
26	–	A	–

Key 1 Compound
2 Experimental example

(No. 2) Leaf experiment on *Phytophthora parasitica*

A chemical solution of 1000 ppm concentration was spread thoroughly on the back of cucumber leaves (variety: Sagami semi-white) and the solution sprayed was air-dried for 1 d, and 10,000 free ascomycetes/mL of *Phytophthora parasitica* cultured with cucumbers were inoculated by applying droplets on 2 locations per leaf, and after holding at 28°C in a dark humid room for 2 d, evaluation was performed based on 4 stages, namely A: no fungus invasion was observed, B: fungus invasion was observed in part of the inoculated sites but the diseased lesions were not expanding and C: fungus invasion was observed in all inoculated sites but no expansion of the diseased lesions to non-inoculated area was observed and D: diseased lesions invaded the

non-inoculated area with the condition equal to the case of non-treatment. Table 6 shows the results.

(No. 3) Pot experiment on *Diaporthe citri*

A chemical solution of 1000 ppm concentration was spread thoroughly in pots of natsu mikan seedlings (Summer tangerine) and the solution sprayed was air-dried for 1 d, and a spore suspension of *Diaporthe citri* (spore concentration (150-fold): 200 spores per vision field) was sprayed and inoculated, and the pots were placed in a 27°C inoculation box for 24 h followed by transferring to a greenhouse; the number of diseased lesions was counted after 2-3 weeks and the rate of diseased leaves and the number of lesions per leaf were counted and evaluation was performed using 3 levels, namely A: inhibitory rate greater than 95%, B: inhibitory rate 50-95% and C: inhibitory rate less than 50%. Table 6 shows the results.

(No. 4) Seedling pot experiment on *Cochliobolus miyabeanus*

Chemical solutions of concentrations shown in Table 7 were spread thoroughly on rice seedlings (variety: Tonewase) in pots and the solution sprayed was air-dried for 1 d, and a spore suspension of *Cochliobolus miyabeanus* (spore concentration (150-fold): 6-8 spores per vision field) was sprayed and inoculated, followed by standing at 25°C in a humid room for 24 h, and the number of diseased lesions per leaf was counted after 1 week and evaluation was performed using 3 levels, namely A: inhibitory rate greater than 95%, B: inhibitory rate 50-95% and C: inhibitory rate less than 50%. Table 7 shows the results.

Table 7

		① 試験例No.-4			① 試験例No.-5			
					② 平均病斑数		③ 発病葉率%	
④ 化合物濃度(ppm)		1000	100	10	100	20	100	20
⑤ 化合物 No.	16	A	B	C	0.7	3.4	41	83
	17	A	C	−	0.6	2.2	15	67
	18	A	A	C	0.4	1.4	9	43
	19	A	B	C	0.8	1.9	31	53
	20	A	C	−	−	−	−	−
	21	A	B	C	0.5	2.1	25	54
	5	A	B	B	0	0.52	0	9.1
⑥ ブランク		−	−	−	1.0		56	

Key
1 Experimental Example
2 Mean number of diseased lesions
3 Rate of diseased leaves
4 Concentration of compound
5 Compound
6 Blank

(No. 5) Pot experiment on *Xanthomonas citri*

Chemical solutions of concentrations shown in Table 7 were spread thoroughly on prescreened natsu mikan (Summer tangerine) in pots with new leaves and the solution sprayed was air-dried for 1 d, and a suspension of *Xanthomonas citri* (concentration: 2 x 10^8 cells/mL) was sprayed and inoculated, followed by standing at 27°C in a humid room for 24 h and then transferred to greenhouse, and the number of diseased lesions was counted after 2-3 weeks and the number of diseased lesions per leaf was determined. Table 7 shows the results.

Effect of the invention

The novel isoquinoline derivatives of the present invention can be utilized as antibacterial agents or insecticides as they are or in certain form of preparations in agricultural and horticultural applications, or they can be utilized as intermediates, rendering them extremely useful compounds.